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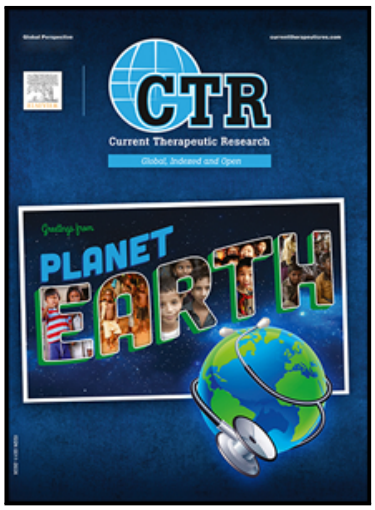

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Feasibility study of Bismuth Subsalicylate (BSS) as an addition to standard of care for COVID-19 therapy

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Dear Editor,

A combination of vaccines and anti-viral drugs is needed to fight SARS-CoV-2. While development and efficacy of SARS-CoV2 vaccines has been timely, utilizing therapeutic anti-viral medications, either repurposed or newly generated will be key. New oral anti-viral medications have been shown to lower hospitalization rates and deaths (1,2). Several repurposed drugs are now being studied with phase 2/ 3 clinical trials (3-5).

Here, we assessed feasibility and tolerability of bismuth subsalicylate (BSS) tablets (Pepto-Bismol) as a 3-day addition to current standard of care treatment (SOC) for mild to moderate SARS-

CoV2 at one clinical site. BSS has been shown to have anti-bacterial and anti-viral activity (6,7). It has been incorporated into medications used for gastrointestinal indications and has been shown to impact SARS-CoV2 replication, specifically its helicase (6-9). This communication provides preliminary data on the clinical feasibility, acceptability of dosing, outcome measures, and staff/patient participation obtained from the initial open label portion (10 patients) of clinical trial NCT04811339.

Recruitment, retention of patients and completion of the initial open label portion were difficult. Patients were enrolled October 2020 – February 2021. Staff shortages due to absence, infection exposure, fatigue and generalized COVID-fear impacted recruitment as well as the required staff/patient connections and sample collections. Forty-four patients were consented, 3 outpatients and 41 inpatients from the COVID-19 floor of the University of Louisville Hospital. Forty-three patients were unvaccinated. Vaccine availability for non-health-care workers and general Kentuckian population under age 70 began March 22 2021. Twenty-five patients did not receive study drug and were excluded due to medication or negative salivary SARS-CoV2 or withdrew due to transportation difficulties or change of mind. Fifteen of these 25 patients only had phone contact with a coordinator.

Nineteen patients received medication. Ten completed the three-day open label study, with no reports of an AE. Of the 9 who did not complete the study, 3 reported an AE, bloating and abdominal discomfort, 5 did not continue BSS after discharge due to transportation/distance issues from hospital affecting saliva/stool collection and 1 was inconclusive for salivary SARS-CoV2 throughout the 3 days. Seventeen of 19 patients receiving drug had personal contact with coordinator. Going forward plans to complete sample acquisition within a 3-hour distance radius need to be in place and mandatory in person coordinator contact needs to be emphasized. One/44 patient became medically unstable between consent and coordinator phone contact and was transferred to ICU.

Completion of 48 BSS tablets was still challenging for the patients who completed the trial. Of the first 5 who completed the study only one finished 48 BSS tablets. In Jan 2021, a protocol amendment was filed to decrease the number of total tablets from 48 to 24. The last 5 patients followed

this dosing regimen. Even with this adjustment the same things impacted full dose completion. Inpatient floor nurses would forget to give BSS tablets and the combination of baseline/day1 visit led to fewer tablets taken the first day. Mandatory daily personal supervision by coordinators with patients and floor nurses needs to be implemented for the randomized placebo-controlled study.

Each day patients recorded their stool frequency, provided stool and saliva samples and scored 5 common COVID-19 symptoms: cough, headache, fatigue, shortness of breath (SOB). Patients were asked by the coordinator (phone or in person) to self-score (from 0-3) the 5 symptoms at baseline/day1 (before BSS), after 24 hours/day 2 and 48 hours/ day3. The final salivary testing and symptom scores were taken prior to last dose of BSS. The primary objective was to measure diarrhea. However, it became apparent after one month that diarrhea was not a typical COVID -19 symptom at our site. Two of 44 consented patients presented with diarrhea and after analysis, stool frequency did not change during the study period. Therefore, after study completion salivary viral clearance (negative RT-LAMP test) along with a patient's daily COVID-19 symptom scores became key assessments. Due to patients' forgetfulness and staff shortage, not all fecal samples were collected. Most limiting was lack of a 4th day of sample collection or scoring. Going forward it will be clearly outlined with staff that final samples and scoring should be carried out 24 hours after completion of final BSS dosing.

Two outpatients and 8 inpatients completed the study; those with incomplete dosing were all inpatients (Table 1). The baseline 5- and 3-symptom patient scores are in Table 1. Hypertension was the most reported pre-existing comorbidity. Pneumonia and/or pleural effusions were the most reported COVID-19-related morbidity. Inpatients took an average of 4 pre-existing medicines and were given an average of 6 new medicines (for COVID-19) in hospital. The two mildly afflicted outpatients were younger, had fewer pre-existing comorbidities but a higher BL COVID-19 symptom score, 7.5 ± 1.5 /15. At the end of the 3-day open-label BSS study the mean overall mean 5-symptom score decreased after 48 hours of drug, Table 1. Cough, headache, and fatigue changed the most during BSS treatment

(Table 1). Seven of 10 patients resolved (score of 0) cough, 3/4 resolved headache and 2/7 decreased perceived fatigue.

Fifty percent of the patients who completed the BSS study became negative for salivary SARS-CoV2 after 48 hours of BSS. The clearance of SARS-CoV2 appears to be related to baseline health status (BHS) and existing home medicines (Figure 1). The BHS score was derived from the number of preexisting comorbidities + number COVID-19- related morbidities + number of baseline COVID-19-related symptoms. One outpatient took 16 tablets in the first 24 hours, felt better, took 4 BSS tablets on day 2 and remained SARS-CoV-2 positive on day 3. This demonstrates key limitations for the study, needed oversight by coordinators for dose completion and final sample collection should be 24 hours after last BSS dose.

Working in the pre-vaccine environment was challenging, however we found that over-the counter BSS could impact viral symptoms and salivary SARS-CoV2 clearance. BSS could be given and tolerated with current SOC COVID-19 treatments. BSS is inexpensive, easily transportable, stored at room temperature, with known safety profile and anti-viral properties. This investigation supports further studies of BSS for COVID-19 .

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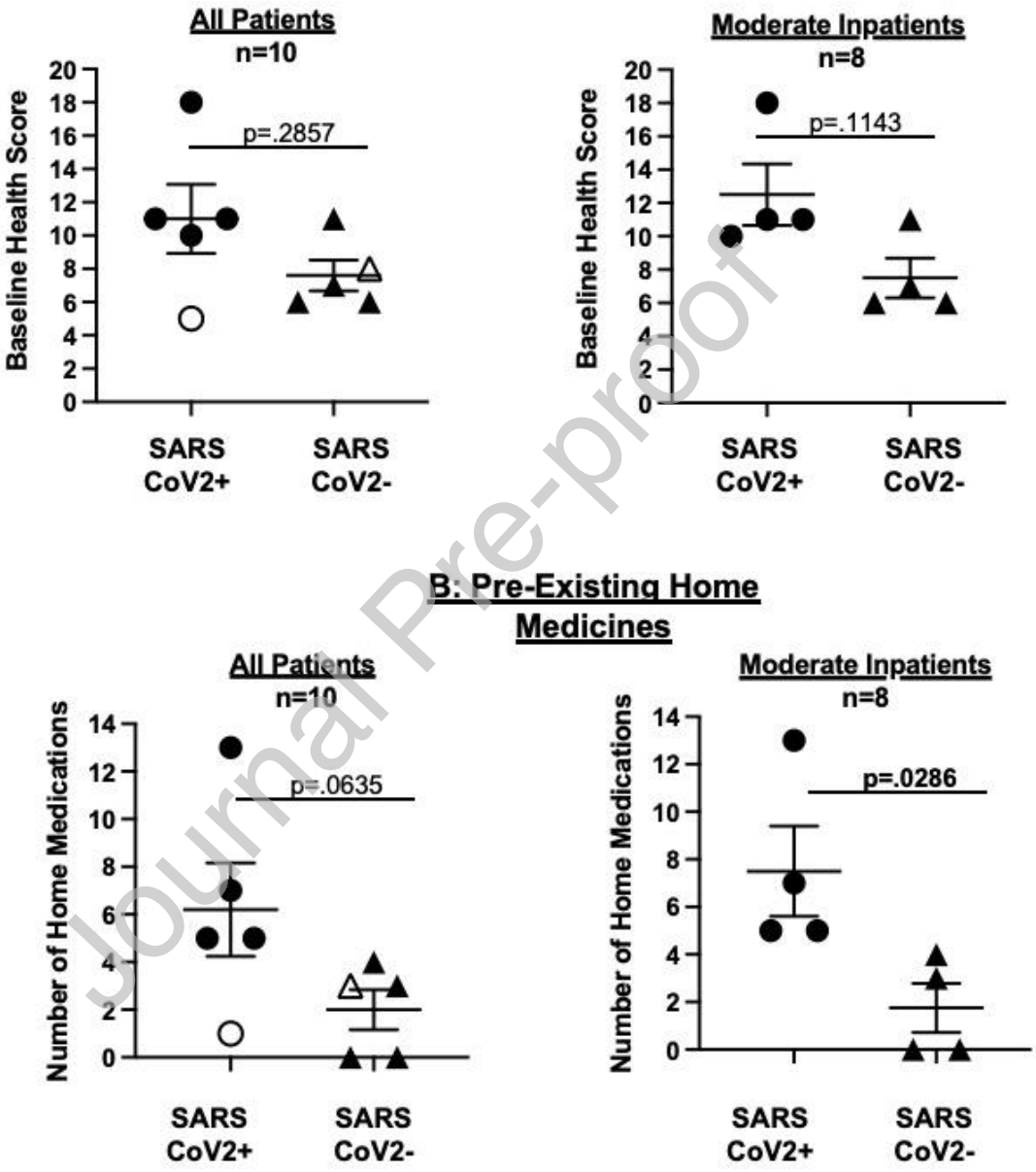
Conflict of Interest Statement

Bruce Yacyshyn: grant funding from P&G; consulting Aerpio Biotechnology, Entrinsic Health Solutions, Inc. and P&G, and speakers bureau Bristol Myers Squibb. Mary Beth Yacyshyn PhD: consulting P&G. James Collins, Michelle Chua, Angela Siegwald, Sara Yacyshyn and Valerie Briones-Pryor: no conflicts. The study sponsor provided the investigational product, but was not involved in protocol development, collection of data, analysis or writing of the manuscript.

Figure 1: SARS-CoV2 status day 3 vs Baseline Health and Medication Status: Figure 1a represents Baseline Health Scores. Baseline Health Scores were calculated by using the sum of the number of preexisting comorbidities + the number of baseline COVID-19-related 5 symptoms + number of COVID-19 morbidities. Figure 1b represents the number of any existing home medications that patients were taking. Open symbols represent outpatients and closed symbols represent inpatients. Statistics were performed using Prism 9 for Mac OS. Nonparametric Mann-Whitney p values were reported.

Figure 1- SARS-CoV2 status Day 3



Declarations of Interest

Bruce Yacyshyn: grant funding from P &G; consulting Aerpio Biotechnology, Entrinsic Health Solutions, Inc. and P & G, and speakers bureau Bristol Myers Squibb. Mary Beth Yacyshyn PhD: consulting P & G.
James Collins, Michelle Chua, Angela Siegwald, Sara Yacyshyn and Valerie Briones-Pryor No conflicts.

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Table 1 Demographics

	Complete BSS (n=10)	Complete BSS Inpatient only (n=8)	Incomplete BSS Inpatient only (n=9)	No BSS (n=25)
Age				
Mean ± s.e.m.	52.7 ± 6.89	59.1 ± 6.83	65.2 ± 2.9	60.6 ± 2.9
Range	(25-78)	(27-78)	(51-79)	(24-84)
BMI				
Mean ± s.e.m.	30.9 ± 2.2	33.3 ± 1.9*	28.7 ± 1.6*	
Range	(21- 44)	(26- 44)	(17-33)	
Gender				
Female	5	4	3	11
Male	5	4	6	14
Race				
Black	2	2	2	7
Caucasian(Hispanic)	1	1	0	1
Native Islander Pacific	0	0	0	1
Caucasian	7	5	7	16
No. of BSS Tablets taken				
Mean ± s.e.m.	27.7 ± 2.8	28.1 ± 3.3	8.1 ± 2.8	NA
Range	(20-48)	(20-48)	(2-28)	
No. of Pre-existing (home) Medicines				
Mean ± s.e.m.	3.8 ± 1.2	4.1 ± 1.5	4.8 ± 1	ND
Range	(0-13)	(0-13)	(1-10)	
No. of new hospital (for COVID-19) Medicines				

Mean ± s.e.m.	NA	5.9 ± 1.1	6.0 ± 0.61	ND
Range		(1-10)	(3-9)	
No. of COVID Symptoms days prior to study entry				
Mean ± s.e.m.	9.4 ± 1.6	10.1 ± 2	12.1 ± 3.0	ND
Range	(5-19)	(5-19)	(6-30)	
No. of Pre-existing Comorbidities				
Mean ± s.e.m.	3.7 ± 1	4 ± 1	4.7 ± 0.5	ND
Range	(0-10)	(0-10)	(3-8)	
No. of COVID morbidities				
Mean ± s.e.m.	3.5 ± 0.9	4.4 ± 0.9	2.4 ± 0.4	ND
Range	(0-9)	(1-9)	(1-4)	
Baseline 5-Symptom Score				
Mean ± s.e.m.	3.8 ± 0.9	2.9 ± 0.7	3.2 ± 1.3	ND
Range	(1-9)	(1-6)	(0-11)	
Day3 5-Symptom Score				
Mean ± s.e.m.	2.9 ± 0.8	2.7 ± 1.0	ND	ND
Range	(0-7)	(0-7)		
Baseline 3-Symptom Score				
Mean ± s.e.m.	2.4 ± 0.5	2.0 ± 0.5	2.1 ± 0.9	ND
Range	(0-5)	(0-4)	(0-8)	
Day3 3-symptom Score				
Mean ± s.e.m.	1.4 ± 0.6	1.5 ± 0.6	ND	ND
Range	(0-4)	(0-4)		

*p=.0464 Nonparametric Mann Whitney test, GraphPad Prism software, version 9.3.1